# Non-invasive respiratory support strategies in COVID-19: conflicting guidelines and limited evidence

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**Introduction**

In hospitalised patients with COVID-19, an increase in oxygen requirements inevitably prompts the clinician to decide how and when to escalate treatment. A key treatment goal is to, where possible, avoid the need for invasive mechanical ventilation (IMV). However up to 20% of hospitalised patients in the UK require admission to critical care units, and around 40% of those requiring IMV for COVID-19 pneumonitis do not survive[1]. To date, the only treatments that have been shown to reduce the need for invasive mechanical ventilation are dexamethasone and IL-6 blockade.

The use of non-invasive respiratory support strategies such as continuous positive airway pressure (CPAP) or high-flow nasal oxygen (HFNO), are attractive treatment options which may avoid the need for IMV and its inherent risks. In the context of COVID-19, concern has been raised that these strategies may cause harm to patients through delays to tracheal intubation or exacerbation of lung injury, to healthcare workers through nosocomial infection, and to healthcare systems through the high oxygen demand of devices.

This uncertain balance of harms and benefits has resulted in marked variation in international practice. A survey of 1132 participants across 85 countries used a case vignette of a previously healthy patient with severe hypoxaemia[2]; choice of initial oxygen strategy included high flow nasal oxygen (47%), CPAP or non-invasive ventilation (NIV) (26%), immediate tracheal intubation (7%), with remaining respondents opting to optimise conventional oxygen therapy.[2] Variability in practice was associated with country, hospital rurality, ICU bed availability, and individual clinician characteristics.

**HFNO, CPAP, or NIV?**

There is a paucity of high-quality evidence for non-invasive respiratory support strategies in COVID-19. Direct evidence remains limited to retrospective case series and cohort studies with inconsistent findings and the inherent risk of bias associated with observational study design[3-5]. For example a recent retrospective study reported failure rates of 66% in COVID-19 patients receiving CPAP, and high mortality (55%) in those requiring IMV after CPAP failure[5]. Evidence for HFNO, CPAP, and NIV as effective treatments for acute hypoxemic respiratory failure (AHRF), are drawn from populations of patients without COVID-19. For example, a recent systematic review and network meta-analysis concluded that NIV delivered by both helmet and mask interface reduced risk of all-cause mortality and tracheal intubation, and HFNO reduced the need for tracheal intubation[6]. However, patient populations in included studies were those presenting with community-acquired pneumonia.

COVID-19 is a novel disease and generalising data from other causes of AHRF is inherently problematic.

In patients with viral influenzae and other coronaviruses, high failure rates of NIV in excess of 70% have been reported[7] such that CPAP or HFNO may serve only to delay, rather than avoid, tracheal intubation. A concern regarding NIV use in patients with more compliant lungs, is the potential for large tidal volume breathing to cause patient self-induced lung injury which has a similar pathogenesis to ventilator-induced lung injury. However the converse argument, is that liberal use of tracheal intubation and mechanical ventilation in COVID-19 is likely to increase ventilator-associated complications and mortality[8].

The risk of nosocomial COVID-19 transmission to healthcare workers delivering non-invasive respiratory support strategies centres on potential aerosol generation. Early evidence from mechanistic evaluations of aerosol and droplet spread suggest the risks of non-invasive strategies are comparable to each other, and to standard oxygen therapy. Generation of aerosols may be influenced by the device, settings and interface, but also other important patient-characteristics factors such as viral load, or coughing profile. However, the lack of substantive evidence does not indicate an absence of risk. Further research is needed to understand the risk to both healthcare workers and other patients.

**Conflicting guidelines**

International guidelines on the management of AHRF and the use of non-invasive respiratory strategies in the context of COVID-19 are prolific (Table 1). In the UK, clinicians may be informed by NHS England and the respiratory and intensive care/anaesthesia communities, as well as global organisations. Across guidelines, there is marked variability in transparency of development, process of synthesising evidence, and recommended approach. For example, NHS England (https://www.nice.org.uk/Media/Default/About/COVID-19/Specialty-guides/specialty-guide-NIV-respiratory-support-and-coronavirus.pdf) recommends CPAP as the preferred form of non-invasive respiratory support in COVID-19 and recommends against HFNO use based on perceived lack of efficacy, oxygen use, and potential infection transmission to healthcare workers. In contrast, Surviving Sepsis Campaign guidelines (https://doi.org/10.1007/s00134-020-06022-5) support the use of HFNO, although it acknowledges that the strength of this recommendation is weak, based on low certainty evidence.

The World Health Organization guidance (https://www.who.int/publications/i/item/clinical-management-of-covid-19) adopts a balanced recommendation, including the use of all non-invasive respiratory support strategies justified by the lack of evidence base available for any individual one. Others, including the Australia and New Zealand Intensive Care Society (ANZICS), have moved away from a previous position of favouring one strategy over another, and now base their recommendations on living guidelines (www.covid19evidence.net.au) that currently suggest decisions regarding non-invasive respiratory support be based on risk assessment of the individual patient and healthcare setting, with an emphasis on reducing the risk of infection transmission to healthcare workers.

**What does this mean for the clinician?**

There is an urgent need for randomised controlled trials to evaluate the effectiveness of non-invasive respiratory support strategies in COVID-19 patients. At present, clinical practice is driven by personal preference and influence, prior experience, and potentially local availability of modalities influenced by logistical concerns in the context of oxygen supplies. But against this backdrop of uncertain evidence on the safety, effectiveness, and optimal approach for AHRF management, it is essential for clinicians to demonstrate equipoise and randomise patients into available clinical trials in their healthcare jurisdictions. As an example there have been a number of reports of pneumomediastinum and pneumothorax in patients with COVID-19, both in patients receiving standard oxygen therapy and in those receiving non-invasive respiratory support[9]. These reports are a cause for concern, although due to their observational nature are confounded by many unmeasured factors. As non-invasive respiratory support is currently being used as part of usual care in many settings in the absence of evidence of harm, such reports further support the need for randomised controlled trials of non-invasive respiratory support in COVID-19 compared to standard care. Clinical trials of non-invasive respiratory support should exclude patients with a contraindication to non-invasive respiratory support and ensure data on harms, such as incidence of pneumomediastinum and pneumothorax, are reported.

By far the largest trial in this area is the UK RECOVERY-Respiratory Support trial[10], funded and prioritised by the National Institute for Health Research as an urgent public health study. This adaptive, randomised controlled, multi-centre trial evaluates the effectiveness of HFNO or CPAP against standard oxygen therapy across hospitalised COVID-19 patients with AHRF, with a primary outcome of tracheal intubation or mortality within 30 days of randomisation. As of February 2021, over 1200 patients have been randomised, and enrolment to the trial features in two UK guidance pathways (Table 1).

During a pandemic, when the demand for critical care resources significantly exceeds the available capacity[11], use of non-invasive respiratory support in an individual patient in the absence of established evidence may be viewed as the only possible treatment, particularly if there is no option to participate in a clinical trial. However, where there are no critical care capacity issues and options to participation in a clinical trial do exist, clinicians should be mindful that provision of this treatment outside the rigorous infrastructure of randomised clinical trials represents random empirical care. In the event one of these interventions is shown to be beneficial, this approach will have delayed answering the urgent clinical question at hand. In the event of an intervention showing no favourable effect (or worse, harm), clinicians will need to justify their continued use of that unproven treatment as part of usual care rather than within a trial framework, as well as their decision to deny patients the opportunity to participate in nationally prioritised research. To understand the most effective non-invasive respiratory support strategy in COVID-19 requires an investigation of the relative benefits and harms to both the patient and the wider healthcare system and this can only be addressed through randomisation to clinical trials. Only in this way will we generate the rigorous data necessary to answer this urgent clinical uncertainty.

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**Conflicts of interest**

All authors declare they are responsible for the conduct and delivery of the RECOVERY-Respiratory Support trial (https://fundingawards.nihr.ac.uk/award/COVID-19-RSC), funded by the National Institute for Health Research (NIHR), and referenced in this manuscript. EG and KC declare no other competing interests. BC reports educational fees from Fisher & Paykel, and her institution receives funds from NIHR for a trial in critically ill patients with acute respiratory failure. BC is a Director of Research for the Intensive Care Society. GDP reports grants from the NIHR. DFM reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis and Eli Lilly, and from sitting on a DMEC for a trial undertaken by Vir Biotechnology. In addition his institution has received funds from grants from several funders for studies in patients with ARDS and COVID-19. In addition, DFM has a patent (US8962032) issued to his institution for a treatment for inflammatory disease. DFM is a Director of Research for the Intensive Care Society and NIHR EME Programme Director.

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Table

**Table 1. Guideline recommendations on non-invasive ventilation strategies for adult patients with COVID-19 acute hypoxaemic respiratory failure**

| | Organisation | Guideline | Overview of non-invasive respiratory strategies* | | |
|---|---|---|---|---|---|
| | | | **HFNO** | **CPAP** | **BIPAP/NIV** |
| **GLOBAL** | | | | | |
| | **World Health Organization** | Clinical management of COVID 19 (May 2020)<br><br>https://www.who.int/publications/i/item/clinical-management-of-covid-19 | Conditional recommendation | Conditional recommendation | Conditional recommendation |
| | **Surviving Sepsis Campaign** | Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) (January 2021)<br><br>https://journals.lww.com/ccmjournal/Abstract/9000/Surviving_Sepsis_Campaign_Guidelines_on_the.95371.aspx | Weak recommendation | Not specifically mentioned | Weak recommendation |
| **UK** | | | | | |
| | **NHS England** | Guidance for the role and use of non-invasive respiratory support in adult patients with COVID-19 (November 2020)<br><br>https://www.nice.org.uk/Media/Default/About/COVID-19/Specialty-guides/specialty-guide-NIV-respiratory-support-and-coronavirus.pdf | Does not support | Supports | Only for hypercapnic acute-on-chronic ventilatory failure |
| | **British Thoracic Society/Intensive Care Society Guidance** | Respiratory care in patients with Acute Hypoxaemic Respiratory Failure associated with COVID-19 (January 2021)<br>https://www.brit-thoracic.org.uk/covid-19/covid-19-information-for-the-respiratory-community/ | Supports (trial enrolment suggested[#]) | Supports (trial enrolment suggested[#]) | Not specifically mentioned |
| | **Faculty of Intensive Care Medicine-Intensive Care Society-Association of Anaesthetists-Royal College of Anaesthetists** | Clinical guide for the management of critical care for adults with COVID-19 during the coronavirus pandemic (October 2020)<br><br>https://icmanaesthesiacovid-19.org/clinical-guide-for-the-management-of-critical-care-for-adults-with-covid-19-during-the-coronavirus-pandemic | Supports in the context of trial enrolment[#] | Supports | Consider for hypercapnic acute-on-chronic ventilatory failure |
| **EUROPE** | | | | | |

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| | **Italian Thoracic Society/Italian Respiratory Society** | Managing the respiratory care of patients with COVID-19 (March 2020)<br><br>https://ers.app.box.com/s/j09ysr2kdhmkcu1ulm8y8dxnosm6yi0h | Supports | Supports | Supports |
| | **Societe de Pneumologie de Langue Francaise** | Procedure for pulmonary management of non-ICU patients hospitalized in the context of the COVID-19 pandemic (April 2020)<br><br>https://splf.fr/covid-19-docs-english-version/ | Conditional recommendation | Conditional recommendation | Conditional recommendation |
| | **Irish Thoracic Society** | Respiratory Management of Patients with COVID-19 (January 2021)<br><br>https://irishthoracicsociety.com/wp-content/uploads/2020/03/Respiratory-Mgt-Guideline-V2-Jan-2021.20.01.pdf | Supports | Supports | Only for hypercapnic acute-on-chronic ventilatory failure |
| | **German Respiratory Society** | Position statement for the State-of-the-Art Application of Respiratory Support in Patients with COVID-19 (June 2020)<br><br>https://www.karger.com/Article/FullText/509104<br><br>German recommendations for critically ill patients with COVID-19 (April 2020)<br><br>https://link.springer.com/article/10.1007/s00063-020-00689-w | Conditional recommendation | Conditional recommendation | Conditional recommendation |
| **AUSTRALIA/NEW ZEALAND** | | | | | |
| | **Australia and New Zealand Intensive Care Society/National COVID-19 Clinical Evidence Taskforce** | COVID-19 Guidelines (January 2021<br><br>https://www.anzics.com.au/coronavirus-guidelines/<br>https://covid19evidence.net.au | Conditional recommendation | Not specifically mentioned | Conditional recommendation |
| **NORTH AMERICA** | | | | | |
| | **Government of Canada** | Clinical management of patients with moderate to severe COVID 19 – interim guidance (August 2020) | Conditional recommendation | Not specifically mentioned | Conditional recommendation |

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| | | https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html | | | |
| | **National Institute of Health (NIH)** | Care of critically ill patients with COVID-19 (December 2020)<br><br>https://www.covid19treatmentguidelines.nih.gov/critical-care/ | Moderate recommendation | Not specifically mentioned | Moderate recommendation |
| **ASIA** | | | | | |
| | **China National Health Commission** | Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (March 2020)<br><br>http://kjfy.meetingchina.org/msite/news/show/cn/3337.html | Supports | Not specifically mentioned | Supports |

*Notes:* *Most recent version of available guidelines used, please refer to links to source documents for full detail. Where documents are available as formal guidelines, specific wording with regards to strength of recommendation are used. Where documents are available as guidance for clinical pathways, use of the term 'Supports' has been used where a modality is included in the content. #Perkins GD, Couper K, Connolly B, et al. RECOVERY- Respiratory Support: Respiratory Strategies for patients with suspected or proven COVID-19 respiratory failure; Continuous Positive Airway Pressure, High-flow Nasal Oxygen, and standard care: A structured summary of a study protocol for a randomised controlled trial. *Trials* 2020;21(1):687. doi: 10.1186/s13063-020-04617-3

*Abbreviations*: HFNO = high flow nasal oxygen, CPAP = continuous positive airway pressure, BIPAP = bilevel positive airway pressure, NIV = non-invasive ventilation